EXHIBIT 8e

C. IN SILICO DATA

ToxCast. The U.S. Environmental Protection Agency along with other regulators (including the FDA) have leveraged substantial expertise and resources in predictive toxicology tools and databases that can aid in filling data gaps about the toxicity and safety of pharmaceuticals and environmental chemicals. The Toxicity Forecasting program (ToxCast) (https://comptox.epa.gov/dashboard/) has combined high throughput libraries of chemicals for screening of environmental chemicals including agrochemicals, orphan drugs, industrial chemicals, food additives, and various other agents such as dyes to create rich datasets to perform predictive toxicology using read-across tools (Williams et al., 2017).

The ToxCast dashboard shows that APAP has potent activity for androgen receptor (AR), nuclear receptor family, in general (inclusive of many hormone receptors including sex steroids and stress hormones), cytochrome P450 enzymes, and finally SOX1 activity which is a developmentally important transcription factor implicated in neurodevelopmental disturbances, respectively (see the table below. Note, APAP has been tested in 979 assays, the four below are the ones in which APAP showed significant "Active" calls. AC50 refers to the concentration at 50% maximum activity, or a measure of relative potency, in micromolar (μM) units).

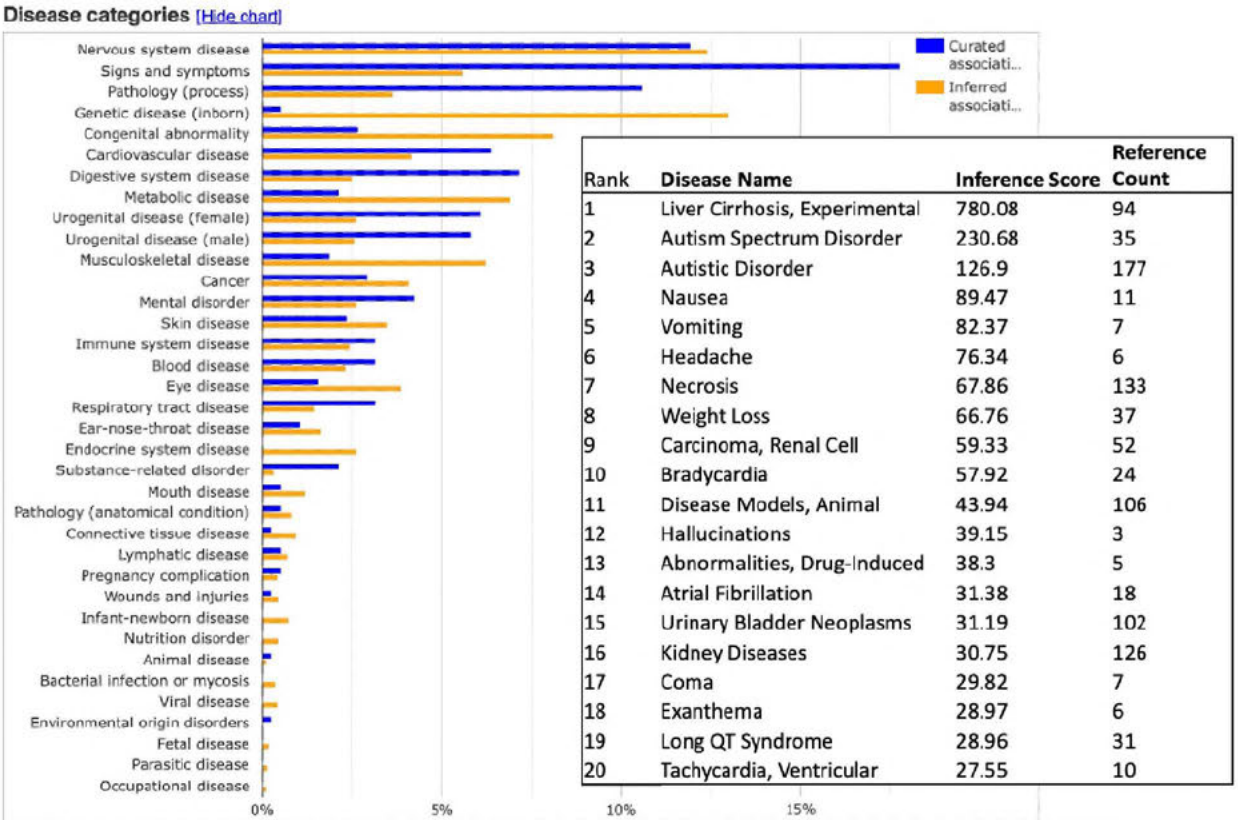
NAME	Description	AC50	INTENDED TARGET FAMILY
UPITT_HCI_U2OS_AR_TIF2_Nucleoli_Antagonist	Data from the assay component UPITT_HCI_U2OS_AR_TIF2_Nucleoli_Antagonist was analyzed into 1 assay endpoint. This assay endpoint, UPITT_HCI_U2OS_AR_TIF2_Nucleoli_Antagonist, was analyzed in the positive fitting direction relative to DHT as the baseline of activity. Using a type of binding reporter, measures of receptor for loss-of-signal activity can be used to understand the binding at the pathway-level as it relates to the gene AR.	0.25116021	nuclear receptor
NVS_NR_hPR	Data from the assay component NVS_NR_hPR was analyzed into 1 assay endpoint. This assay endpoint, NVS_NR_hPR, was analyzed in the positive fitting direction relative to DMSO as the negative control and baseline of activity. Using a type of binding reporter, loss-of-signal activity can be used to understand changes in the binding as they relate to the gene PGR. Furthermore, this assay endpoint can be referred to as a primary readout, because the performed assay has only produced 1 assay endpoint. To generalize the intended target to other relatable targets, this assay endpoint is annotated to the "nuclear receptor" intended target family, where the subfamily is "steroidal".	14.3629481	nuclear receptor
LTEA_HepaRG_CYP1A1_up	Change in transcription factor expression relative to control (delta-delta-ct) for HepaRG cell cultures in an induction preparation. The adherent cells have some metabolic capability. Expression measured by inducible reporter assay using Fluidigm qRT-PCR to monitor. Suffix _up indicates curve fitting for increase in expression (induction).	34.0111873	cyp

ATG_Sox_CIS_up	Data from the assay component ATG_Sox_CIS was analyzed into 1 assay endpoint. This assay endpoint, ATG_Sox_CIS_up, was analyzed in the positive fitting direction relative to DMSO as the negative control and baseline of activity. Using a type of inducible reporter, measures of mRNA for gain-of-signal activity can be used to understand the reporter gene at the transcription factor-level as they relate to the gene SOX1. Furthermore, this assay endpoint can be referred to as a primary readout, because this assay has produced multiple assay endpoints where this one serves a reporter gene function. To generalize the intended target to other relatable targets, this assay endpoint is annotated to the dna binding intended target family, where the subfamily is HMG box protein.	85.3541036	dna binding

The Comparative Toxicogenomics Database. Integration of data across studies and data resources is challenging. Researchers at North Carolina State University, with funding and support of the NIH, generated the Toxicogenomics Database (CTDbase.org) to integrate knowledge across domains about genetics, exposures, model systems, and other lines of evidence that renders a powerful tool for evidence mapping, systems biology, discovery, disease relevance and literature discovery. The CTDbase is a publicly available, government-funded resource that collects and integrates information from scientific literature to provide insights into the relationships between chemicals, genes, diseases, and other biological entities. It serves as a valuable tool for researchers, scientists, and anyone interested in understanding the molecular mechanisms underlying toxicological and environmental health effects.

CTDbase can be searched by chemical (or gene, or disease, and so forth) and fully orthogonal types of data linking to the other domains are linked and clickable from one's search. When searching CTDbase for disease links for APAP, the results show, based on gene pathway involvement, expected hepatic targets but also strong neurodevelopment (autism, ASD) enrichment.

In the results for APAP, below disease categories on left show nervous system disease as a top if not the top category. Results of the top 20 tabular specific enrichments are shown in the inset to the right. Rank 2 and 3 are autism or ASD. These connections show enriched inference scores that are based on strength of network enrichments vs a background of random networks. Put more plainly, the inference score refers to a scoring system used to evaluate the strength of evidence supporting the association between a specific chemical and a particular biological event or outcome.



Rank	Disease Name	Inference Score	Reference Count
1	Liver Cirrhosis, Experimental	780.08	94
2	Autism Spectrum Disorder	230.68	35
3	Autistic Disorder	126.9	177
4	Nausea	89.47	11
5	Vomiting	82.37	7
6	Headache	76.34	6
7	Necrosis	67.86	133
8	Weight Loss	66.76	37
9	Carcinoma, Renal Cell	59.33	52
10	Bradycardia	57.92	24
11	Disease Models, Animal	43.94	106
12	Hallucinations	39.15	3
13	Abnormalities, Drug-Induced	38.3	5
14	Atrial Fibrillation	31.38	18
15	Urinary Bladder Neoplasms	31.19	102
16	Kidney Diseases	30.75	126
17	Coma	29.82	7
18	Exanthema	28.97	6
19	Long QT Syndrome	28.96	31
20	Tachycardia, Ventricular	27.55	10

Figure 43. Results for APAP search in ctdbase.org. Curated chemical–disease data were retrieved from the Comparative Toxicogenomics Database (CTD), MDI Biological Laboratory, Salisbury Cove, Maine, and NC State University, Raleigh, North Carolina. World Wide Web (URL: http://ctdbase.org/). [June, 2023]

Line of Evidence	Reliability	Relevance	Weight Assigned
In silico	LOW to MEDIUM	LOW	LOW

Reliability is assessed as LOW to MEDIUM because the computational terms are defined and linked through rigorous statistical tools, but they are dependent upon user and study-defined investigations, assays, or publication trends. Relevance is set to LOW as a in silico enrichments or activity calls in high throughput data have several major limitations in modeling human health and disease. Therefore, overall weight is assigned as **LOW**.

XIII. WOE SUMMARY RISK CONCLUSION

Line of Evidence	Reliability	Relevance	Weight Assigned	Signal
In Silico	LOW to MEDIUM	LOW	LOW	Positive
In Vitro/ Ex Utero	HIGH	MEDIUM	MODERATE	Positive
In Vivo	MEDIUM	HIGH	MODERATE to HIGH	Positive

All lines of evidence have positive signals. APAP increases the risk of adverse neurodevelopmental outcomes in humans when used in accordance with the dosing information on the product label.

XIV. CONCLUSIONS

As discussed above, it is my opinion to a reasonable degree of scientific certainty based on my analysis of the weight of the evidence in this case as described above that APAP is a developmental neurotoxicant capable of causing neurodevelopmental disorders in both humans and animals. While epidemiological studies may have confounders that must be controlled for, preclinical animal models are not confounded in the same way because the test subjects can be isolated from confounding variables.

Further, the heterogeneity of the results is not a reason to dismiss the effects of APAP shown in these individual studies. First, the effects of APAP on the body are so complex and multifaceted that no single study design could capture them all. In addition, preclinical evidence of APAP neurodevelopmental toxicity does not require uniformity in design, dose, or hepatic involvement or noninvolvement in order to present relevant data. Though individual studies may show mixed or bidirectional results, neurodevelopmental perturbation of prenatal APAP can manifest in various ways in terms of directionality. In addition, preclinical toxicology data is often inconsistent, even in a regulatory context (Leuchtefeld et al., 2018). Even in straightforward toxicological endpoints under relatively strict regulatory designs, results are not fully consistent across labs. This principle is especially true in realms like developmental neurotoxicology, which is far from straightforward. The heterogeneity of ultimate endpoints seen in the preclinical studies described in this report makes sense given the context of the extremely delicate cascading cellular processes disturbed by APAP use. This heterogeneity is also present in human observational studies, which have shown other neurodevelopmental issues, including hyperkinetic disorders, also associated with APAP use. In brief, preclinical studies show that prenatal APAP perturbs a wide array of cascading neurodevelopmental processes, which are complex enough to cause heterogeneous outcomes depending on inter-subject variability, timing of exposure, and other factors.

I have reviewed internal documents from JJCI wherein results of certain preclinical studies are discounted, criticized, or deemed invalid because the findings were in the presence of liver toxicity or because liver toxicity was not measured. However, there are several reasons that

criticism is unfounded. Most importantly, hepatoxicity can occur even with APAP use at therapeutic doses (Vitols, 2013; Sabaté et al., 2011; Kearns et al., 1998). APAP hepatotoxicity is incompletely understood (Hinson et at., 2010), thus, creating a single delineation between no toxic hepatic involvement and toxic hepatic involvement is naïve under such equivocal understandings, and given that this organ is a primary site of xenobiotic metabolism that stresses the organ under therapeutic and supratherapeutic doses alike.

Internal documents show that the manufacturers of APAP products and their contractors were intensely critical of any toxicology study that failed to show dose-response. Certainly, requiring that there is dose-response is a classic toxicology feature and is more important when there are concerns about causality. However, the stance that studies which did not examine a dose-response relationship should be discounted or discredited is inappropriate for multiple reasons. First, when all other variables are held constant, there are no concerns about the causal relationship between the drug and the outcome in a single dose toxicological study. In addition, numerous high quality preclinical in vivo studies are performed with single concentrations of a chemical (e.g., Church et al., 2018; Cui et al., 2022) demonstrating that a lack of dose-response data is not an indicator of poor-quality research. In other words, the preference towards data showing a dose-response relationship must be viewed in its proper context. Dose-response in preclinical research is less critical when the substance being tested is, like APAP, one that has been used hundreds of times in vivo in rodent studies and has been on the market as an over-the-counter pharmaceutical for nearly a century. Finally, requiring a dose-response relationship to be demonstrated in every single toxicology study ignores the reality that the labs performing these studies, unlike Johnson & Johnson, have relatively limited resources and may not be able to exponentially multiply the cost of their studies in order to examine the effects of multiple doses on individual subjects. Many of the studies criticized for failure to show a dose-response effect were not designed to show such an effect, nor should their results be dismissed for that reason. Instead, those studies should be viewed in context as part of a comprehensive body of evidence showing APAP's potential to act as a developmental neurotoxicants.

Certain preclinical studies may have weaknesses based on the route used for administration of APAP (*e.g.*, criticisms of subcutaneous or peritoneal injection and gavage). Though there is a possibility of those types of administration causing stress in the treated animals, the fact that controls are administered in the same manner undermines that argument. Further, APAP is administered by injection (subcutaneous and intravenous) to people. Additionally, the route of administration can affect the T_{max} and C_{max} APAP (IV administration led to earlier peak concentrations and higher concentrations in brain) but generally does not markedly affect the area under the curve (AUC highly overlapping in ranges) in both plasma and cerebrospinal fluid (see Singla et al., 2012). Though the route of administration should be considered when reviewing the results of a particular study, the fact that APAP was not orally administered does not result in a nullity of the findings.

The documents I have reviewed from the manufacturers of APAP appear to attempt to decontextualize the studies, attacking individual research teams in a vacuum for sometimes petty shortcomings including spelling errors. However, it is my opinion that the preclinical research on this topic must be viewed as a whole in order to undergo a rigorous weight of evidence analysis. When viewed in that context, the evidence that APAP harms neurodevelopment is overwhelming.

Despite ample evidence of neurotoxicity in preclinical studies, which stretch back to as early as the 1980s, as well as observational human studies, APAP continues to be sold and recommended to pregnant women with no specific warning regarding its potential effects on neurodevelopment. In addition, it appears that despite multiple opportunities to do so, the primary manufacturers of APAP never undertook their own vigorous preclinical review, nor did they do their own preclinical studies to attempt to prove neurodevelopmental safety of the drug.

The foregoing opinions are substantively identical to the opinions stated in my June 16, 2023 report. All opinions offered herein are held to a reasonable degree of scientific certainty.

Dated: June 21, 2023

Respectfully submitted,

Brandon L. Pearson, MS, PhD